Remarks

Claim 11 has been amended. New claim 29 has been added. Upon entry of this paper, claims 11, 12-18, 20, and 27-29 will be pending and under consideration.

Support for the amendments to claim 11 can be found, for example, in claims 20 and 21 as originally filed. Support for new claim 29 can be found, for example, in the Examples appearing on pages 14-31 (see first full paragraph on page 15, and the second full paragraph on page 22) of the application as originally filed. Applicant believes that the aforementioned amendments to claim 11 and new claim 29 introduce no new matter. The outstanding rejections are addressed in the order in which they appear in the Office action.

Rejections under 35 U.S.C. § 112, Second Paragraph

According to page 2 of the outstanding Office action, claims 11-18, 20, 27 and 28 presently stand rejected under 35 U.S.C. § 112, second paragraph. The Office maintains the rejection that the term "an effective amount" is indefinite because the specification in the paragraph bridging pages 12 and 13 discusses administering midazolam for inducing rapid sedation, anxiolysis, amnesia, or anesthesia. Applicant submits that the same paragraph states "an effective amount of benzodiazepine [this includes midazolam] or other compound includes the amount effective to achieve the relief of palliation of symptoms, condition and/or diseases that need benzodiazepine therapy." Applicant submits that, based on this text, the term "effective amount" would be understood by those skilled in the art. Nevertheless, in order to promote prosecution, Applicant has amended claim 11 to recite that the midazolam or salt thereof, when administered intranasally to a mammal, is capable of inducing rapid sedation, anxiolysis, amnesia or anesthesia. In view of the amendment to claim 11 and, therefore, the claims depending from claim 11, Applicant respectfully requests that this rejection be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 103

According to the Office action, (i) claims 11, 13, 15, 18, 20 and 28 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over Patent No. 5,166,202 to Schweizer (the '202 Patent) in view of U.S. Patent No. 6,565,832 B1 to Haslwanter (the '832 Patent), (ii) claims

14 and 18 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over the '202 Patent and the '832 Patent and further in view of U.S. Patent No. 5,554,639 to Craig (the '639 Patent), (iii) claim 12 presently stands rejected under 35 U.S.C. § 103(a) as being obvious over the '202 Patent and the '832 Patent and further in view of the '639 Patent [it appears that the Office meant U.S. Patent No. 5,789,375 to Mukae (the '375 Patent) rather than the '639 Patent], and (iv) claims 16, 17, 20 and 28 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over the '202 Patent and the '832 Patent and further in view of Fisgin *et al.* (2000) J. Child Neurol. 15:833-835 (Fisgin). Applicant respectfully traverses these rejections in view of the foregoing amendments and following remarks.

The '202 Patent discusses a method of treating a panic disorder and panic attacks, and in the prevention of panic attacks, by administering midazolam or a pharmaceutically acceptable salt thereof. (See Abstract.) In the '202 Patent, the midazolam could be administered nasally. (See the Example appearing on Col. 4, lines 41-53.) The '202 Patent, however, fails to teach or suggest administering a formulation comprising midazolam or a salt thereof, combined with from about 15% to about 25% by volume of polyethylene glycol and propylene glycol. Furthermore, in the Example provided in the '202 Patent, the midazolam was administered at a concentration of 5 mg/mL ("one drop delivered 0.05 ml, which contained 0.25 mg of midazolam" – see Col. 4, lines 48-49.) This is particularly relevant for new claim 29, which further states that the composition comprises no less than 25 mg/mL of midazolam or a pharmaceutically acceptable salt thereof.

The '832 Patent describes an aqueous-based sprayable composition comprising a therapeutic or palliative agent, water and a mixture of microcrystalline cellulose and alkali metal carboxyalkylcellulose. (See Abstract.) The '832 Patent states that "[d]epending upon the intended application, it may be desirable to incorporate up to about 10% by weight, more typically about 0.5 to about 5 weight percent, of an additional rheology-modifying agent, such as a polymer or other material. Useful materials include, ... polyethylene glycols" (See Col. 4, lines 20-29.) Nevertheless, the '832 Patent fails to disclose an intranasal formulation comprising (i) midazolam or a salt thereof, (ii) about 15% to about 25% by volume of polyethylene glycol, and (iii) propylene glycol. If anything, Applicant submits that the '832 Patent, by teaching up to

10 % by weight, more typically about 0.5 to about 5 weight percent, of a rheology-modifying agent, in effect teaches away from using about 15% to about 25% by volume of polyethylene glycol. Applicant submits that the presence and amount of polyethylene glycol in a liquid formulation affects the viscosity and surface tension of the resulting formulation, and that both properties have a profound effect on the sprayability of an intranasal formulation, which in turn affects the efficiency of intranasal drug delivery.

The '639 Patent describes medicaments contains 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5 methanesulfonamide sulphate salt (2:1) and pharmaceutically acceptable solvates thereof. The '639 Patent indicates that the solutions may contain "water and a physiologically acceptable co-solvent (for example, ethanol, propylene glycol, polyethylene glycols such as PEG 400). (See Col. 2, lines 55-57.) At the outset, Applicant submits that the active ingredient in the '639 Patent is not midazolam, and, excipients effective at solubilizing one active ingredient may not be effective in solubilizing a different active ingredient. Furthermore, the '639 Patent fails to disclose a formulation containing about 15% to about 25% by volume of polyethylene glycol and propylene glycol. The '639 Patent fails to disclose using a combination of polyethylene glycol and propylene glycol, and further fails to describe using 15% to about 25% by volume of polyethylene glycol.

The '375 Patent describes a pernasal composition containing a pharmacologically active substance (peptide hormones), water, and an alcohol, wherein the alcohol content is 10-70 vol. % of the whole composition. (See abstract.) The '375 Patent notes that the alcohol, among other things, can be propylene glycol. (See Col. 3, line 61.) Furthermore, '375 Patent notes that the composition can include, for example, a thickener or gelling agent including among other things, polyethylene glycol. (See Col. 5, line 27.) Nevertheless, the '375 Patent fails to describe a composition containing an active ingredient other than a peptide, for example, a peptide hormone. More specifically, the '375 Patent fails to disclose a formulation containing midazolam. Furthermore, the '375 Patent also fails to disclose a formulation containing 15% to about 25% by volume of polyethylene glycol.

Fisgin describes intranasally administering a 5 mg/mL solution of midazolam to sixteen children. (See Abstract.) Fisgin fails to describe a formulation containing 15% to about 25% by

volume of polyethylene glycol and propylene glycol. The Fisgin solution contained 5 mg/mL midazolam. This is relevant for new claim 29, which further recites the composition comprises no less than 25 mg/mL midazolam or a salt thereof.

Assuming for the sake of argument only that the skilled artisan would have been motivated to combine the references in the manner suggested by the Office, Applicant submits that the combined teachings of the applied references fail to teach or suggest the claimed subject matter, taken as a whole. For example, none of the references teach a composition – never mind a midazolam containing composition – containing 15% to about 25% by volume of polyethylene glycol. Accordingly, the applied references, even when combined, fail to teach each and every element of the claimed invention. For this reason alone, Applicant submits that the applied references, either alone or in combination, fail to render the claimed invention obvious.

Furthermore, of the references applied by the Office, only the '202 Patent and Fisgin describe midazolam containing compositions. The Office then combines the teachings of, for example, the '202 Patent, with other references that describe excipients useful in formulating active ingredients other than midazolam. For example, the '832 Patent describes a number of active ingredients other than midazolam, the '375 Patent describes peptides, for example, peptide hormones, and the '639 Patent describes 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5 methanesulfonamide sulphate salt (2:1). Applicant submits that the choice of excipients for formulating the active ingredients in the '832 Patent, the '375 Patent, and the '639 Patent may not necessarily be extrapolated to compositions where midazolam is the active ingredient. In other words, it is not apparent that a formulation optimized for the delivery of one active ingredient can be used to optimize the delivery of a second, different active ingredient. Accordingly, Applicant submits that, at the time the invention was made, there was no reason to believe that midazolam could be formulated with 15% to about 25% by volume of polyethylene glycol and propylene glycol to produce a composition, which when administered intranasally would be effective in inducing rapid sedation, anxiolysis, amnesia or induction of anesthesia.

New claim 29, which depends from claim 11, also requires that the midazolam or the pharmaceutically acceptable salt thereof be present in the liquid composition at a concentration of no less than 25 mg/mL. Although the '202 Patent and Fisgin describe formulations containing

midazolam, as noted above, both references only describe solutions containing 5mg/mL midazolam. Applicant submits that the skilled artisan relying on the combined teachings of the '202 Patent, Fisgin, or any of the applied references, would have no reason to believe that it would be possible to produce an intranasal formulation containing no less than 25 mg/mL midazolam or a salt thereof, which when administered intranasally would be effective in inducing rapid sedation, anxiolysis, amnesia or induction of anesthesia.

For at least the reasons noted above, Applicant submits that the claimed invention would not have been obvious to the skilled artisan relying on the teachings of the applied references, either alone or in combination, and Applicant respectfully requests that this rejection be reconsidered and withdrawn.

Double Patenting

According to pages 7-10 of the outstanding Office action, claims 11-18, 20, 27 and presently stand rejected for obviousness-type double patenting over certain claims of U.S. Patent No. 6,610,271. Applicant respectfully requests that this rejection be held in abeyance until the instant claims are considered in condition for allowance but for this double patenting rejection. At that time, Applicant plans to file a terminal disclaimer, if the double patenting rejection is still considered to be appropriate.

Conclusion

Applicant believes that, in the view of the above amendments and comments, the pending claims are in condition for allowance. Early favorable action is respectfully solicited. The Office is invited to contact the undersigned with any questions about this submission.

Respectfully submitted,

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